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MINTZ LEVIN COHN FERRIS GLOVSKY & POPEO ONE FINANCIAL CENTER BOSTON, MA 02111			THOMAS, DAVID C	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/767,899	<b>Applicant(s)</b> BERKA ET AL.
	<b>Examiner</b> DAVID C. THOMAS	<b>Art Unit</b> 1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 09 December 2008.

2a) This action is FINAL.      2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1-3,6-29 and 32-44 is/are pending in the application.

4a) Of the above claim(s) 16-21,23 and 35-44 is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 1-3,6-15,22,24-29 and 32-34 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date: _____
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date: _____	6) <input type="checkbox"/> Other: _____

**DETAILED ACTION**

1. Applicant's response filed December 9, 2008 is acknowledged. Claims 1, 14, 22 and 34 (currently amended) and 2, 3, 6-13, 15, 24-29, 32 and 33 (original or previously presented) will be examined on the merits. Claims 16-21, 23 and 35-44 were previously withdrawn and claims 4, 5, 30 and 31 were previously canceled.

***Claim Rejections - 35 USC § 103***

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-3, 6-14, 22, 24, 25, 32 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths (U.S. Patent No. 2002/0119459) in view of Andreadis

et al. Nucleic Acids Res. (2000) 28:e5, pp. i-viii) and further in view of Wangh et al. (U.S. Patent Pub. No. 2004/0053254).

Griffiths teaches a method for amplifying one or more nucleic acids onto a bead (DNA or RNA in microcapsules can be amplified by various methods, paragraph 23, lines 5-10 and paragraph 98, lines 1-22) comprising the steps of:

- (a) forming a water-in-oil emulsion to create a plurality of aqueous microreactors (emulsion has a water phase containing the biomolecules and an inert hydrophobic phase of oil, paragraph 91, lines 14) wherein at least one of the microreactors comprises one single stranded nucleic acid template (microcapsules contain, on average, one or fewer genetic elements each, including RNA, paragraph 81, lines 1-12, paragraph 98, lines 1-3 and paragraph 125, lines 1-6), and an amplification reaction solution comprising a population comprising a plurality of molecules of the first primer species and a plurality of molecules of a second primer species and reagents necessary to perform nucleic acid amplification wherein the first primer species is capable of binding to the single stranded nucleic acid template and the second primer species is capable of binding to a complementary strand of the single stranded nucleic acid template (nucleoside triphosphates and other necessary reagents are required in the microcapsules for amplification reactions such as PCR or those involving transcription steps and requiring two primers for binding the target and complementary strands, paragraph 98, lines 1-23, paragraph 100, lines 1-6 and paragraph 101, lines 1-8);  
(b) amplifying the single stranded nucleic acid template and the complementary strand to the template in the amplification reaction solution to form a population of

Art Unit: 1637

amplified copies of the single stranded template nucleic acid (DNA or RNA in microcapsules can be amplified by various methods including PCR using one of the primers as a biotinylated primer, paragraph 98, lines 1-23, paragraph 110, lines 1-5 and paragraph 217, lines 1-11); and

(c) binding a plurality of the amplified copies of the single stranded template nucleic acid to the bead in the microreactor (nucleic acids amplified using biotinylated primers can be captured onto microbeads coated with avidin, paragraph 110, lines 1-5 and paragraph 111, lines 1-10);

(d) breaking the aqueous microreactors to release at least one of the nucleic acid bound beads and the amplification reaction solution comprising unbound amplification products (microcapsules containing genetic elements such as nucleic acid templates bound to beads, along with amplification reaction mixtures, may be broken for purposes of pooling the templates comprising the genetic elements, paragraph 168, lines 1-6); and

(e) recovering the nucleic acid bound beads (reagents may be added which bind to or react with the bead-bound nucleic acids and their products, to enrich for the genetic elements with modified optical properties, paragraphs 168-171; product-bound nucleic acids can also be reacted with antibodies in the microcapsules before pooling of the tagged nucleic acids by breaking the microcapsules, paragraph 172, lines 1-16).

With regard to claim 2, Griffiths teaches a method for amplifying one or more nucleic acids wherein a majority of the microreactors include a single nucleic acid

Art Unit: 1637

(microcapsules contain, on average, one or fewer genetic elements each, paragraph 81, lines 1-12).

With regard to claim 3, Griffiths teaches a method for amplifying one or more nucleic acids wherein said amplification reaction solution is a polymerase chain reaction solution further comprising nucleotide triphosphates, a thermostable polymerase, and a buffer compatible with polymerase chain reaction conditions (NTPs and other necessary reagents are required in the microcapsules for enzymatic reactions, paragraph 100, lines 1-6 and 101, lines 1-8; PCR can be used if the emulsions are thermostable, paragraph 98, lines 18-23).

With regard to claims 6 and 7, Griffiths teaches a method for amplifying one or more nucleic acids wherein said emulsion additionally contains emulsion stabilizers (emulsions may stabilized by addition of one or more surface-active agents or surfactants such as Span 80, paragraph 92, lines 1-11).

With regard to claims 8 and 9, Griffiths teaches a method for amplifying one or more nucleic acids wherein said emulsion is heat stable to 95°C (emulsions can be made to work under PCR conditions, paragraph 98, lines 18-23).

With regard to claim 10, Griffiths teaches a method for amplifying one or more nucleic acids wherein amplification is carried out by a method of transcription-based amplification (transcription of the DNA to amplify the nucleic acid copies, paragraph 98, lines 1-12).

With regard to claim 11, Griffiths teaches a method for amplifying one or more nucleic acids wherein the emulsion is formed by the dropwise addition of the nucleic

Art Unit: 1637

acid templates, beads, and amplification reaction solution into an oil (droplets of microscopic or colloidal size of aqueous phase are added to hydrophobic oil phase, paragraph 90, lines 1-6 and paragraph 91, lines 1-9).

With regard to claims 12 and 13, Griffiths teaches a method for amplifying one or more nucleic acids performed with at least 50,000 nucleic acids (reactions that contain on average one nucleic molecule and one bead (paragraph 23, lines 5-14), contain about  $10^9$  beads in suspension and therefore as many as  $10^9$  copies of the nucleic acid, paragraph 300, lines 5-13, paragraph 301, lines 1-4, and paragraph 302, lines 1-2).

With regard to claim 14, Griffiths teaches a method of amplifying nucleic acid in a microreactor such as a water-in-oil emulsion wherein the emulsion droplets range from 0.1 to 10  $\mu\text{m}$  in diameter (paragraph 103, lines 1-6).

With regard to claim 22, Griffiths teaches a method for amplifying a nucleic acid onto a bead comprising the steps of:

(a) providing one single stranded nucleic acid template to be amplified (one genetic element such as RNA is provided in each microcapsule, paragraph 125, lines 1-6);

(b) providing a solid support material comprising a generally spherical bead having a diameter about 2 to about 40  $\mu\text{m}$ , wherein the bead comprises a plurality of molecules of a first population of a first primer species disposed thereon capable of binding to the nucleic acid template (paramagnetic beads containing avidin coating in order to bind nucleic acid are about 5  $\mu\text{m}$  in diameter, paragraph 111, lines 4-10; one of

the PCR primers can be biotinylated and therefore capable of binding to the avidin-coated beads, paragraph 110, lines 1-5);

(c) mixing the nucleic acid template and the bead in an amplification reaction solution comprising a plurality of molecules of a second population of the first primer species (such as biotinylated primer at allow binding of the products to avidin-coated beads, paragraph 110, lines 1-5), a second primer species and reagents necessary to perform a nucleic acid amplification reaction in a water-in-oil emulsion, wherein the first primer species is capable of binding to the single stranded nucleic acid template and the second primer species is capable of binding to a complementary strand of the single stranded nucleic acid template (nucleoside triphosphates and other necessary reagents are required in the microcapsules for amplification reactions such as PCR or those involving transcription steps and requiring two primers for binding the target and complementary strands, paragraph 98, lines 1-23, paragraph 100, lines 1-6 and paragraph 101, lines 1-8);

(d) amplifying the single stranded nucleic acid template and the complementary strand of the single stranded nucleic acid template in the amplification reaction solution using the second population of the first primer species and the second primer species to form a population of amplified copies of the single stranded template nucleic acid (DNA or RNA in microcapsules can be amplified by various methods including PCR using one of the primers as a biotinylated primer, paragraph 98, lines 1-23, paragraph 110, lines 1-5 and paragraph 217, lines 1-11); and

(e) binding a plurality of the amplified copies of the single stranded template nucleic acid to the bead in the microreactor (nucleic acids amplified using biotinylated primers can be captured onto microbeads coated with avidin, paragraph 110, lines 1-5 and paragraph 111, lines 1-10); and

(f) recovering the nucleic acid bound beads (reagents may be added which bind to or react with the bead-bound nucleic acids and their products, to enrich for the genetic elements with modified optical properties, paragraphs 168-171; product-bound nucleic acids can also be reacted with antibodies in the microcapsules before pooling of the tagged nucleic acids by breaking the microcapsules, paragraph 172, lines 1-16).

With regard to claim 24, Griffiths teaches a method for amplifying one or more nucleic acids further comprising the step of enriching for beads which bind amplified copies of the nucleic acid away from beads to which no nucleic acid is bound, the enrichment step consisting of cell sorting (beads which contain fluorescent signals due to amplification and subsequent binding of groups involved in generating fluorescent signal can be sorted by flow cytometry, paragraph 202, lines 1-14).

With regard to claim 25, Griffiths teaches a method for amplifying one or more nucleic acids wherein the enrichment step is performed by affinity purification with magnetic beads that bind nucleic acid (enrichment steps can be performed using magnetic beads and a magnet, paragraph 239, lines 34-45).

With regard to claim 32, Griffiths teaches a method for amplifying one or more nucleic acids further comprising the steps of:

separating the template carrying beads and magnetic bead (such as by flow sorting, paragraph 202, lines 1-14; and

removing the magnetic beads with a magnetic field (enrichment steps can be performed using magnetic beads and a magnet, paragraph 239, lines 34-45).

With regard to claim 33, Griffiths teaches a method for amplifying one or more nucleic acids wherein the separating is achieved by incubating the template carrying beads and the magnetic beads in a solution with a basic pH (solution containing beads were suspended in buffer containing 5 mM Tris 7.4 prior to transcription, translation and flow cytometry and incubated at 43°C, paragraph 238, lines 1-10).

Griffiths does not teach methods of amplifying a nucleic acid wherein two populations of a first primer species are used, one bound to a solid surface such as a bead, and the other in an amplification reaction solution with a second primer species, wherein the molecules of the second primer species and the molecules of the first population of the first primer species are each present in greater numbers within the aqueous microreactors than the number of molecules of the second population of the first primer species and wherein substantially all of the molecules of the second population of the first primer species in the reaction solution are depleted. Griffiths also does not teach a method wherein a plurality of copies of the single stranded template nucleic acid are bound to the first population of the first primer species on the bead and wherein a bead-bound complementary strand is extended from the first primer species. Griffiths also does not teach microreactors having an average size of 50 µm in diameter.

Art Unit: 1637

Andreadis teaches a method for producing covalently immobilized DNAs on beads that can be used for *in vitro* transcription/translation reactions (see Abstract) by performing PCR using a bead-bound forward primer and a reverse primer in solution and also a small concentration of the forward primer in solution (p. iii, lines 10-22 and p. vi, lines 6-9) to generate PCR products in solution that will in turn bind to the immobilized primer to increase production of the bead-bound product (p. vi, lines 9-12 and 49-53).

Wangh teaches a method of performing non-symmetric PCR using one amplification primer that is present at a concentration at least five times greater than the other primer such that the limiting primer can be used to exhaustion (paragraph 25, lines 1-22 and paragraph 30, lines 1-7). Wangh also teaches a method wherein one of the primers, the limiting one or the primer in excess, is fixed to a solid matrix such as a bead (paragraph 181, lines 1-7).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Griffiths for amplifying nucleic acids in a microcapsule such as a water-in-oil emulsion on the surface of a bead contained within the emulsion with the methods of Andreadis and Wangh for performing asymmetric PCR using two populations of a first primer, one attached to a solid surface and one in lower concentration in solution, since the primer in solution can be used to exhaustion to perform the initial rounds of amplification on the target nucleic acid in combination with the second primer (Wangh, paragraph 25, lines 1-22), while the

Art Unit: 1637

resulting extension products can be further amplified in the solid-phase to generate products immobilized on the bead (Andreadis, p. vi, lines 9-12 and 49-53). Furthermore, an ordinary practitioner would have been motivated to use an asymmetric PCR assay as taught by Andreadis and Wangh using one of the primers affixed to a bead surface since the assay not only is highly suited for detecting low levels of target sequence in small reaction volumes (Wangh, paragraph 32, lines 1-8), but the extension products will remain attached to the bead or other solid surface for direct use in a variety of downstream applications (Andreadis, p. viii, lines 30-33 and Wangh, paragraph 181, lines 1-7). Furthermore, the asymmetric PCR methods of Andreadis and Wangh are easily adaptable to performing in microcapsules such as water-in-oil emulsion droplets since such microcapsules are sufficiently large to accommodate any conditions or reaction requirements for amplification reactions such as PCR (Griffiths, paragraph 98, lines 18-23 and paragraph 100, lines 1-6). Moreover, the use of microcapsules allows reactions to be compartmentalized to separate different target sequences from each other, yet targets at very low copy number can still be readily amplified (Griffiths, paragraph 81, lines 1-16).

It would also have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use emulsion droplets of larger sizes such as in the range of 50  $\mu\text{m}$  as used by the applicant or in the range of 10  $\mu\text{m}$  as used by Griffiths since these differences in emulsion droplet size would not be expected to greatly alter the conditions for amplification. Though the effective concentration of a single template DNA would be lower in the larger droplets, this would be offset by the larger absolute

Art Unit: 1637

amounts amplification reagents such as nucleotides and primers. This is consistent with the Federal Circuit decision in *In re Peterson*, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003) "We have also held that a *prima facie* case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties." Thus, an ordinary practitioner would have recognized that the droplet size could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions  
of a claim are disclosed in the prior art, it is  
not inventive to discover the optimum or workable  
ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of droplet size was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. As noted, a skilled artisan would expect droplet sizes of 10-50  $\mu\text{m}$  to have nearly identical properties in the amplification of nucleic acids. Thus, an ordinary practitioner would have recognized that the results could be adjusted to maximize the desired results.

5. Claims 15 and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths (U.S. Patent No. 2002/0119459) in view of Andreadis et al. Nucleic Acids

Art Unit: 1637

Res. (2000) 28:e5, pp. i-viii) and further in view of Wangh et al. (U.S. Patent Pub. No. 2004/0053254) as applied to claims 1-3, 6-14, 22, 24, 25, 32 and 33 above, and further in view of Jurinke et al. (U.S. Patent No. 6,303,309).

Griffiths, Andreadis and Wangh together teach the limitations of claims 1-3, 6-14, 22, 24, 25, 32 and 33 as discussed above.

Neither Griffiths nor Andreadis nor Wangh teach a method for amplifying one or more nucleic acids wherein more than 10,000 or at least 1,000,000 amplification copies of each target nucleic acid molecule are bound to each bead. In addition, neither Griffiths nor Andreadis nor Wangh teach a method for amplifying one or more nucleic acids wherein the beads are sepharose beads.

Jurinke teaches a method of purification of biotin-labeled PCR products by complexing the products to a solid support containing a biotin-binding compound such as streptavidin immobilized on the surface, including agarose, sepharose, or magnetic beads (column 8, lines 49-60). Jurinke also teaches immobilization of 100 pmol biotinylated oligodeoxynucleotide to 50 µl (~40 million) streptavidin-coated magnetic beads (column 8, 12, lines 13-16), which represents about 1 million molecules bound per bead.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Griffiths, Andreadis and Wangh for amplifying nucleic acids on a bead within a microcapsule such as a water-in-oil emulsion using a non-symmetric PCR with that of Jurinke for purification of PCR

Art Unit: 1637

products using solid-supports such as magnetic or sepharose beads since the use of such beads, because of the stability of the biotin-streptavidin complex, allows further purification and extensive washing to remove all excessive reaction components prior to final recovery of the final PCR product (Jurinke, column 8, lines 61-67). Thus, an ordinary practitioner would have been motivated to use magnetic or sepharose beads as taught by Jurinke for binding and purifying PCR or other amplification products generated in a microreactor since these beads have a large capacity and high affinity for such products, especially when using highly stable binding pairs such as biotin and streptavidin to form complexes of the amplification products on the beads.

6. Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths (U.S. Patent No. 2002/0119459) in view of Andreadis et al. Nucleic Acids Res. (2000) 28:e5, pp. i-viii) and further in view of Nakano et al. (J. Biotech. (2003) 102:117-124).

With regard to claim 34, Griffiths teaches a method for producing a clonal population of nucleic acids, comprising:

(a) providing a single stranded nucleic acid template to be amplified (one genetic element, such as RNA, is provided in each microcapsule, paragraph 81, lines 1-12, paragraph 98, lines 1-3 and paragraph 125, lines 1-6);

(b) mixing the single stranded nucleic acid template and the beads in an amplification reaction solution that comprises a second population of a plurality of molecules of the first primer species (such as a biotinylated primer to allow binding of the products to avidin-coated beads, paragraph 110, lines 1-5), a plurality of molecules

Art Unit: 1637

of a second primer species and reagents necessary to amplify the nucleic acid template, wherein the first primer species is capable of binding to the single stranded nucleic acid template and the second primer species is capable of binding to a complementary strand of the single stranded nucleic acid template (nucleoside triphosphates and other necessary reagents are required in the microcapsules for amplification reactions such as PCR or those involving transcription steps and requiring two primers for binding the target and complementary strands, paragraph 98, lines 1-23, paragraph 100, lines 1-6 and paragraph 101, lines 1-8); and

(c) forming an emulsion to create a plurality of microreactors (emulsion has a water phase containing the biomolecules and an inert hydrophobic phase of oil, paragraph 91, lines 14) comprising the nucleic acid template, beads, and the amplification reaction solution, wherein at least one of the microreactors comprises a single nucleic acid template (microcapsules contain, on average, one or fewer genetic elements each, paragraph 81, lines 1-12 and paragraph 125, lines 1-6) and a single bead encapsulated in the amplification reaction solution (nucleic acid may be linked to one or more magnetic beads, paragraph 23, lines 5-10), wherein the microreactors are contained in the same vessel (such as a microtiter plate or microfuge tube, paragraph 290, lines 1-5 and paragraph 291, lines 1-9).

Griffiths does not teach methods of amplifying a plurality of nucleic acid templates from 50-800 bp in length, wherein two populations of a first primer species are used, one bound to a solid surface such as a bead, and the other in an amplification reaction solution with a second primer species, wherein the molecules of the second

Art Unit: 1637

primer species and the molecules of the first population of the first primer species are each present in greater numbers within the aqueous microreactors than the number of molecules of the second population of the first primer species. Griffiths also does not teach a method wherein a plurality of copies of the single stranded template nucleic acid are bound to the first population of the first primer species on the bead and wherein a bead-bound complementary strand is extended from the first primer species.

Andreadis teaches a method for producing covalently immobilized DNAs on beads that can be used for in vitro transcription/translation reactions (see Abstract) by performing PCR using a bead-bound forward primer and a reverse primer in solution and also a small concentration of the forward primer in solution (p. iii, lines 10-22 and p. vi, lines 6-9) to generate PCR products in solution that will in turn bind to the immobilized primer to increase production of the bead-bound product (p. vi, lines 9-12 and 49-53).

Nakano teaches a method of PCR in water-in-oil emulsions using a plurality of templates of 528 and 512 bp in size (p. 118, column 2, line 39 to p. 119, column 1, line 8).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Griffiths and Andreadis for amplifying nucleic acids on a bead within a microcapsule such as a water-in-oil emulsion using an asymmetric PCR with that of Nakano since Nakano also teaches a method for amplifying multiple nucleic acids in water-in-oil emulsions that is easily

Art Unit: 1637

adaptable to the methods of Griffiths and Andreadis using a bead to bind amplification products in the emulsion. Thus, an ordinary practitioner would have been motivated to use the combined system of Griffiths, Andreadis and Nakano for amplifying multiple nucleic acid targets of different sizes in an emulsion containing a bead using an asymmetric PCR process since the products can easily be purified simultaneously on the same bead and later separated by sizing methods or simply analyzed by gel electrophoresis (Nakano, see Figure 2).

***Response to Arguments***

7. Applicant's additional arguments with respect to the previous rejections of record have been noted, but are moot in view of the rejection of the claims based on new grounds.

***Summary***

8. Claims 1-3, 6-15, 22, 24-29 and 32-34 are rejected. No claims are allowable.

***Conclusion***

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

***Correspondence***

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320 and whose fax number is 571-273-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should

Art Unit: 1637

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David C Thomas/  
Examiner, Art Unit 1637

/Kenneth R Horlick/  
Primary Examiner, Art Unit 1637